

5.01 FRUQUINTINIB, Capsule 1 mg, Capsule 5 mg, Fruzaqla[®], Takeda Pharmaceuticals Australia Pty. Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Authority Required (STREAMLINED) listing for fruquintinib for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with or who are not considered candidates for fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus trifluridine/tipiracil (TRI/TIP) (Table 1).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with mCRC who have been previously treated with or are not considered candidates for fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.
Intervention	Fruquintinib 5 mg once daily for 21 days, followed by 7 days off to complete a 28-day cycle.
Comparator	TRI/TIP 35 mg/m ² /dose based on the trifluridine component twice daily on Days 1-5 and Days 8-12 of a 28-day cycle.
Outcomes	PFS, OS, time to worsening of ECOG PS and safety.
Clinical claim	In patients with mCRC, who have been previously treated with or are not considered candidates for fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy, fruquintinib provides non-inferior OS and PFS, and a non-inferior safety profile compared to TRI/TIP.

Source: Table 1-1, p15 of the submission.

ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; mCRC = metastatic colorectal cancer; OS = overall survival; PFS = progression-free survival; TRI/TIP = trifluridine/tipiracil; VEGF = vascular endothelial growth factor.

2 Background

Registration status

- 2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate's Overview was available.
- 2.2 Fruquintinib is being evaluated under an Orbis-Access hybrid collaboration pilot pathway (Project Orbis and Access New Active Substance Work-Sharing Initiative). The proposed TGA indication is:

“For the treatment of adult patients with mCRC who have been previously treated with or are not considered candidates for available therapies, including

fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and an anti-epidermal growth factor receptor (EGFR) therapy.”

- 2.3 In November 2023, fruquintinib was granted approval by the Food and Drug Administration (FDA) under Project Orbis for adult patients with mCRC who had received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy. The FDA’s approval was based on the results from two double-blind, placebo-controlled, randomised trials of fruquintinib, FRESCO 1 and FRESCO 2. Given the differences in prior therapy and patient population (single country; China), the FDA did not consider the FRESCO 1 trial to be an adequate stand-alone trial to support the approval of fruquintinib. However, based on the results from the FRESCO 1 trial, the FDA considered that treatment with fruquintinib provided a clinically meaningful survival benefit for patients who were refractory to standard therapy. Although FRESCO 2 studied fruquintinib in a more refractory setting after disease progression on additional anticancer agents, in the context of the totality of the evidence, the FDA considered that the requested indication was supported (p18, FDA Multi-disciplinary Review and Evaluation).
- 2.4 In April 2024, fruquintinib was granted marketing authorisation by the European Medicines Agency (EMA) for adult patients with mCRC who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either TRI/TIP or regorafenib. The ESC noted that, in contrast to the proposed TGA and approved FDA indications, the EMA supports the use of fruquintinib in patients following TRI/TIP (unless intolerant or received prior regorafenib) rather than replacing/displacing TRI/TIP.
- 2.5 Following Advisory Committee on Medicines (ACM) advice, the TGA Delegate proposed to approve the registration of fruquintinib for the requested indication. The Delegate noted that the advice of the ACM committee supports this approach regarding the indication wording, which is also aligned with the approach taken by FDA. The Delegate noted that infection and hepatotoxicity should be added as identified risks to the Risk Management Plan, and pancreatitis should be added as a potential risk for pharmacovigilance monitoring.

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Requested listing

- 3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№. of Rpts	Available brands
FRUQUINTINIB					
fruquintinib 5 mg capsule, 21	NEW	1	21	5	Fruzaqla®
fruquintinib 1 mg capsule, 21	NEW	4	84	5	Fruzaqla®
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative advice: A patient may only qualify for PBS-subsidised treatment under this restriction once. Following completion of the initial PBS-subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.					
Indication: Metastatic colorectal cancer					
Treatment Phase: Initial PBS-subsidised treatment					
Clinical criteria: Patient must have/had a WHO performance status of 1 or less, prior to initiation of treatment with this drug for this condition.					
AND					
Clinical criteria Patient must not have previously received <i>PBS-subsidised treatment with this drug</i> for this condition; OR Patient must be each of: (i) currently receiving non-PBS subsidised supply for this drug for this PBS indication, (ii) untreated with this drug at the time that non-PBS subsidised supply was commenced, (iii) free of disease progression since commencing non-PBS subsidised supply					
AND					
Clinical criteria: Patient must have previously received treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-vascular endothelial growth factor (anti-VEGF) agent and an anti-epidermal growth factor receptor (anti-EGFR) agent for this condition; OR Patient must not be a suitable candidate for treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGF agent and an anti-EGFR agent for this condition,					
AND					
Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition.					
Prescribing Instructions: The patient's WHO performance status and body weight must be documented in the patient's medical records at the time the treatment cycle is initiated.					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined					
Administrative Advice:					

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No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Indication: Metastatic colorectal cancer
Treatment Phase: Continuing <i>treatment</i>
Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition.
AND
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition <i>Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition</i>
AND
Clinical criteria: Patient must not have developed disease progression while receiving treatment with this drug for this condition <i>Patient must not develop progressive disease whilst receiving PBS-subsidised treatment with this drug for this condition</i>

3.2 The requested restriction was aligned with that of TRI/TIP for the treatment of mCRC. The requested restriction was consistent with the FRESCO 1 trial (used as a supportive clinical trial), in which patients had previously received and failed at least two standard chemotherapy lines for mCRC; however, it was not consistent with the inclusion criteria of the FRESCO 2 trial (used as the main clinical trial). In FRESCO 2, patients were required to have progressed on or been intolerant to TRI/TIP or regorafenib, in addition to having received two prior lines of therapy.

3.3 The requested restriction did not restrict use of fruquintinib to a specific line of treatment (i.e., third line (3L, i.e. replacing or displacing 3L TRI/TIP) or fourth line (4L, i.e. used subsequent to 3L TRI/TIP)). Similarly, the restriction for TRI/TIP does not limit its use to the 3L setting. The Pre-sub-committee response (PSCR) stated that the totality of the clinical evidence for fruquintinib supports 3L use (FRESCO 1 trial) and 4L use (FRESCO 2 trial), i.e. for all patients who will be eligible under the proposed 3L (or later) restriction. The ESC agreed with the evaluation that the requested line of listing has implications for the choice of comparator and the economic and financial estimates, requiring different considerations for each treatment line.

For more detail on PBAC’s view, see section 7 PBAC outcome.

4 Population and disease

4.1 In Australia, there were approximately 15,367 new cases of colorectal cancer (8,133 males and 7,234 females) and 5,307 deaths (2,810 males and 2,497 females) in 2023.¹

¹ Australian Institute of Health and Welfare (2023), Cancer data in Australia, AIHW, Australian Government, accessed 20 March 2024. Available at: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/summary-dashboard>

Around 18% of colorectal patients are diagnosed with mCRC (Stage IV). The prognosis for mCRC is poor, with a 5-year relative survival rate of 13%.²

- 4.2 Fruquintinib is a highly selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR) 1, -2, and -3, resulting in antitumor effects including suppression of tumour angiogenesis and lymph angiogenesis, thereby inhibiting tumour growth and metastasis.
- 4.3 The European Society for Medical Oncology (ESMO) guidelines for mCRC in July 2023 recommend TRI/TIP ± bevacizumab (BEVA) or regorafenib in the third- and subsequent-lines of treatment (noting that fruquintinib is not included).³ However, an updated recommendation in November 2023 from ESMO indicates that TRI/TIP + BEVA may also be used in earlier lines of therapy following oxaliplatin and irinotecan regimen failure.⁴ The US National Comprehensive Cancer Network (NCCN) guidelines for Colon Cancer and Rectal Cancer recommend fruquintinib, regorafenib, and TRI/TIP ± BEVA for patients with mCRC who have progressed through standard therapies, with the combination of TRI/TIP + BEVA preferred over TRI/TIP alone.⁵
- 4.4 The submission proposed fruquintinib be used for adult patients with mCRC who have been previously treated with or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy and/or an anti-EGFR therapy (i.e., those moving to 3L treatment).

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated TRI/TIP as the comparator. TRI/TIP is the only PBS-listed treatment option for patients with mCRC who have been treated previously or are not considered suitable for current available therapies, and most likely to be replaced by fruquintinib. In November 2021, the PBAC considered TRI/TIP to be the reasonable comparator for this population when considering regorafenib (paragraph 5.2, regorafenib Public Summary Document (PSD), November 2021 PBAC Meeting).
- 5.2 Other treatment options for mCRC, including regorafenib and TRI/TIP + BEVA, were identified by the submission but were not considered to be comparators. Regorafenib has previously been considered for mCRC (November 2021) and hepatocellular carcinoma (July 2019), and not recommended by the PBAC for either indication. While

² Australian Institute of Health and Welfare (2018), Colorectal and other digestive-tract cancers, AIHW, Australian Government, accessed 20 March 2024. Available at: <https://www.aihw.gov.au/getmedia/892d43f7-ab5d-48fe-9969-129f138687f3/aihw-can-117.pdf?v=20230605165443&inline=true>

³ <https://www.esmo.org/living-guidelines/esmo-metastatic-colorectal-cancer-living-guideline/advanced-and-metastatic-disease-without-potential-conversion/advanced-and-metastatic-disease-without-potential-conversion/third-and-further-lines>

⁴ [https://www.annalsofoncology.org/article/S0923-7534\(23\)04335-1/fulltext](https://www.annalsofoncology.org/article/S0923-7534(23)04335-1/fulltext)

⁵ https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

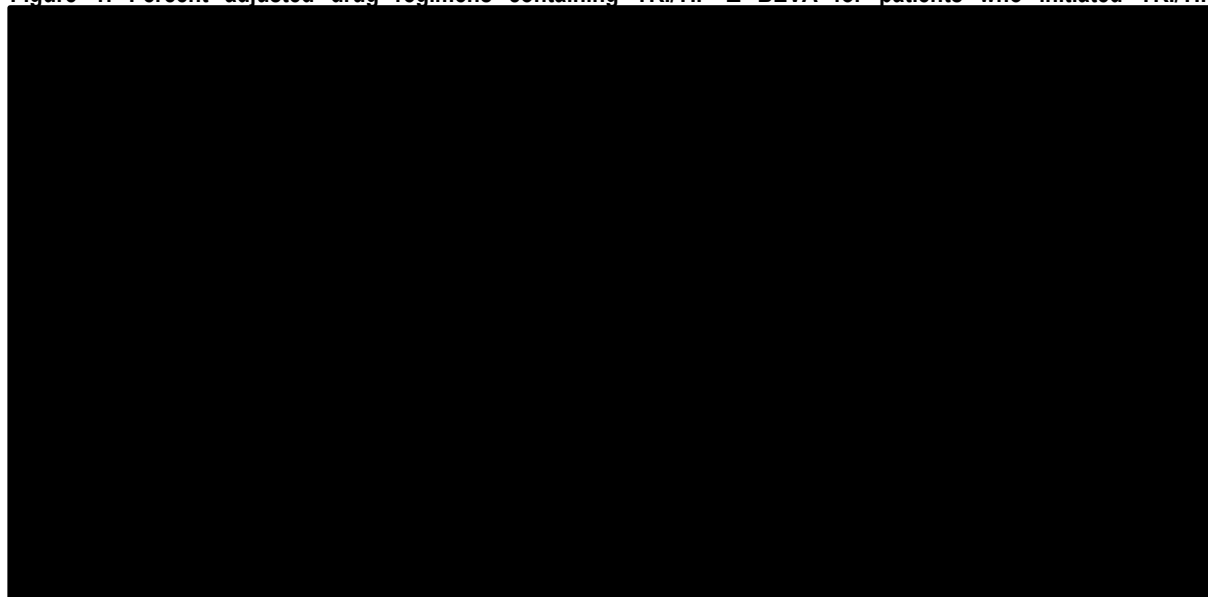
the TGA indication for TRI/TIP does not preclude its use with other medicines such as BEVA, its PBS restriction states, 'The treatment must be the sole PBS-subsidised therapy for this condition'.

5.3 The evaluation agreed with the submission that it was appropriate not to consider regorafenib to be a comparator. However, the evaluation noted that TRI/TIP + BEVA could be considered an additional comparator for the following reasons:

- The results from the phase III randomised SUNLIGHT trial⁶ demonstrated that TRI/TIP + BEVA was associated with statistically significant improvement in overall survival (OS) over TRI/TIP alone (hazard ratio [HR] = 0.61; 95% confidence interval [CI]: 0.49, 0.77), and the combination was approved by the FDA based on this trial.
- Recent data from DUSC for the period December 2018 to December 2023 indicates that despite the wording of the TRI/TIP restriction (as the sole PBS-subsidised therapy), PBS-listed BEVA is currently being utilised alongside TRI/TIP for mCRC in clinical practice in Australia. Figure 1 shows that the percentage of patients on this combination treatment reached a high of █% in October 2023, with the most recent data available (week beginning 31 December 2023) showing █% of patients on the combination. The ESC noted that a substantial number of patients may be accessing BEVA for use in combination with TRI/TIP outside of the PBS.
- The NCCN Colon Cancer and Rectal Cancer guidelines recommend fruquintinib, regorafenib, and TRI/TIP ± BEVA for the treatment of mCRC that has progressed through standard therapies (paragraph 4.3), implying that TRI/TIP ± BEVA could be a comparator to fruquintinib if both drugs are used in the same line of treatment (e.g., 3L), and indicating that TRI/TIP + BEVA is the preferred regimen over TRI/TIP alone.

⁶ Prager et al., Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. *The New England Journal of Medicine* 2023; 388, 1657-1667.

Figure 1: Percent adjusted drug regimens containing TRI/TIP ± BEVA for patients who initiated TRI/TIP



Source: Analysis conducted by the Drug Utilisation Sub Committee (DUSC).

- 5.4 If fruquintinib is to be considered as an alternative to TRI/TIP ± BEVA (i.e., in the 3L setting), the FRESCO 1 trial, a randomised trial conducted in China, provides the most relevant evidence regarding the efficacy and safety of fruquintinib in this setting. However, a potential applicability issue for an Australian population was that the trial only enrolled Chinese patients. If fruquintinib is to be used after TRI/TIP ± BEVA (i.e., in the 4L setting), the most appropriate comparator would be best supportive care (BSC). The FRESCO 2 trial, an international and multi-regional study, evaluated the efficacy and safety of fruquintinib compared to placebo (BSC) in patients who had progressed on or were intolerant to TRI/TIP (or regorafenib, or both). The PSCR reiterated that an evidence base exists for both the proposed 3L setting (FRESCO 1) and the 4L setting (FRESCO 2), which is a strength of the submission (see also paragraph 3.3), noting that FRESCO 2 is an RCT of fruquintinib vs BSC following TRI/TIP (or regorafenib).
- 5.5 The PSCR maintained that TRI/TIP + BEVA is not an appropriate comparator because:
- The combination is not PBS listed;
 - TRI/TIP's PBS listing specifies usage as the sole PBS subsidised therapy for mCRC;
 - TRI/TIP + BEVA regimen has never been assessed for cost-effectiveness by PBAC;
 - Although there appears to be some use of TRI/TIP + BEVA shown in the DUSC data presented by the evaluation, the vast majority of TRI/TIP use is in the monotherapy setting.
 - The PBAC Guidelines (v5.0) for choosing a comparator state that "If the proposed medicine is likely to replace listed PBS medicines, the relevant comparator would be a medicine prescribed on the PBS to treat that target population".

- 5.6 However, the ESC noted that the PBAC Guidelines (v5.0) also state the following:

Choosing the medicine most likely to be replaced

Where there is more than one comparator, the main comparator should be the therapy that prescribers would most replace with the proposed medicine. The PBAC bases its judgment about the main comparator on what would be likely to happen, rather than what should happen, in keeping with the above approach to the main comparator.

The ESC also noted the recent increasing use of TRI/TIP + BEVA, according to the DUSC data, since the SUNLIGHT trial results became available in 2023, and that BEVA may be being accessed by some patients with private scripts.

- 5.7 Given that there is uncertainty that all sources utilised in the submission (i.e., treatment guidelines and proposed/current PBS restrictions) are consistently referring to the same number of prior therapies, for the purposes of this document, 3L therapy with fruquintinib refers to its use replacing or displacing TRI/TIP ± BEVA, and 4L therapy with fruquintinib refers to its use subsequent to TRI/TIP ± BEVA, rather than those exact lines of therapy.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.3 Comments from 2 health care professionals described the lack of effective later-line treatment options for patients with mCRC and noted the potential for fruquintinib in addressing this gap. One respondent noted their patient is responding well to fruquintinib treatment.
- 6.4 The PBAC noted the advice received from 3 organisations (Bowel Cancer Australia, Rare Cancers Australia, and the Medical Oncology Group of Australia [MOGA]) supporting the PBS listing of fruquintinib for the treatment of patients with mCRC. Bowel Cancer Australia stated that fruquintinib could benefit up to 800 Australians with metastatic bowel cancer each year by improving median overall survival and noted that the oral formulation made the treatment accessible and manageable for many patients. Rare Cancers Australia stated that the PBS listing of fruquintinib would significantly reduce the financial burden of patients having to self-fund this treatment. The PBAC noted that the MOGA presented a European Society for Medical Oncology

Magnitude of Clinical Benefit Scale (ESMO-MCBS) for fruquintinib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement),⁷ based on a comparison with TRI/TIP.

Clinical trials

6.5 No head-to-head trials were available comparing fruquintinib to TRI/TIP for mCRC. The submission was based on two indirect treatment comparisons (ITCs) between fruquintinib and TRI/TIP, using placebo as the common reference:

- The main ITC compared fruquintinib (via the FRESCO 2 trial) with TRI/TIP (via the RECOURSE trial). The trials were nominated for the main ITC in the submission because they were closely aligned and considered representative of the proposed PBS population, being large international studies conducted primarily in a Caucasian demographic. However, data from the FRESCO 2 trial is not the most appropriate for the comparison between fruquintinib and TRI/TIP because fruquintinib patients were required to have already failed TRI/TIP and/or regorafenib.
- A sensitivity ITC of efficacy compared fruquintinib (via a meta-analysis of FRESCO 2, FRESCO 1, and 2012-013-00CH1 trials) with TRI/TIP (via a meta-analysis of the RECOURSE, TERRA, and J003 trials). The submission did not present an ITC for safety using the safety outcomes from all trials.

6.6 The PBAC previously considered results from the RECOURSE and J003 trials as part of the TRI/TIP submission in November 2016 and the regorafenib submission in November 2021. Although results from the TERRA trial were not included in the TRI/TIP submission, they were considered in the regorafenib submission to the PBAC in November 2021.

6.7 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Fruquintinib trials		
FRESCO 2 (NCT04322539)	A global, multicentre, randomised, placebo-controlled phase 3 trial to compare the efficacy and safety of fruquintinib plus best supportive care to placebo plus best supportive care in patients with refractory metastatic colorectal cancer (FRESCO-2) final analysis clinical study report Dasari, A., Lonardi, S. et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study.	February 2023 <i>The Lancet</i> 2023; 402 (10395), 41-53.
	Dasari, A., Sobrero, A. et al. FRESCO-2: A global Phase III study investigating the efficacy and safety of fruquintinib in metastatic colorectal cancer.	<i>Future Oncology</i> 2021; 17(24), 3151-3162.

⁷ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017]

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Trial ID	Protocol title/ Publication title	Publication citation
	Desari, A., Yao, J. et al. FRESKO-2: A global phase III study of the efficacy and safety of fruquintinib in patients (pts) with metastatic colorectal cancer (mCRC).	<i>Journal of Clinical Oncology</i> 2021; 39 (3 SUPPL).
	Dasari, A., Lonardi, S. et al. FRESKO-2: A global phase III multiregional clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer.	<i>Annals of Oncology</i> 2022; 33 (S7), S1391-S1392.
	Sobrero, A., Dasari, A. et al. Health-related quality of life (HRQoL) associated with fruquintinib in the global phase 3, placebo-controlled, double-blind FRESKO-2 study.	<i>Journal of Clinical Oncology</i> 2023; 41(4), 67.
	Yoshino, T., Dasari, A. et al. 46MO FRESKO-2: A global / multiregional phase III clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with metastatic colorectal cancer.	<i>Annals of Oncology</i> 2022; 33 (S9), S1446-S1447.
FRESKO 1 (NCT02314819)	A Randomized, Double-blind and Placebo-controlled Phase III Trial Comparing Fruquintinib Efficacy and Safety vs Best Support Care (BSC) in Advanced Colorectal Cancer Patients Who Have Failed at Least Second Lines of Chemotherapies Li, J., Guo W. et al. Safety Profile and Adverse Events of Special Interest for Fruquintinib in Chinese Patients with Previously Treated Metastatic Colorectal Cancer: Analysis of the Phase 3 FRESKO Trial. Li, J., Qin S. et al. FRESKO: A Phase III trial evaluating Fruquintinib efficacy and safety in 3+ line colorectal cancer patients. Li, J., Qin, S. et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer the FRESKO randomized clinical trial.	May 2017 <i>Advances in Therapy</i> 2020; 37(11): 4585-4598. <i>Journal of Clinical Oncology</i> 2017; 35(15). <i>Journal of the American Medical Association</i> 2018; 319(24): 2486-2496.
2012-013-00CH1 (NCT02196688)	A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase II Clinical Study Comparing Fruquintinib Plus Best Supportive Care (BSC) And Placebo Plus BSC In Patients With Advanced Colorectal Cancer Who Have Failed To Respond To Second-Line And Above Standard Chemotherapy. Xu, R., Li, J. et al. Safety and efficacy of fruquintinib in patients with previously treated metastatic colorectal cancer: a phase Ib study and a randomized double-blind phase II study. Li, J., Xu, R. et al. A randomized, double-blind, placebo-controlled, multicentre Phase II clinical trial of fruquintinib in patients with metastatic colorectal cancer (mCRC).	February 2016 <i>Journal of Haematology and Oncology</i> 2017; 10(1): 22. <i>European Journal of Cancer</i> 2015; 51: S366.
Trifluridine/tipiracil trials		
RECOURSE (NCT01607957)	Mayer, R., Custem, E. et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer.	<i>The New England Journal of Medicine</i> 2015; 372(20), 1909–1919.
	Yoshino, T., Mayer, R. et al. Results of a Multicenter, Randomized, Double-Blind, Phase III Study of TAS-102 vs. Placebo, with Best Supportive Care (BSC), in Patients (PTS) with Metastatic Colorectal Cancer (MCRC) Refractory to Standard Therapies (RECOURSE).	<i>Annals of Oncology</i> 2014; 25, ii114.
TERRA (NCT01955837)	Xu J., Kim, T. et al. Results of a randomized, double-blind, placebo-controlled, phase III trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: the TERRA study.	<i>Journal of Clinical Oncology</i> 2018; 36(4), 350-358.
	Kim TW, Shen L, Xu JM et al. TERRA: a randomized, double- blind, placebo-controlled phase 3 study of TAS-102 in Asian patients with metastatic colorectal cancer.	<i>Annals of Oncology</i> 2016; 27 (6), vi153.
J003 (JapicCTI-090880)	Yoshino T, Mizunuma N, Yamazaki K et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial.	<i>The Lancet Oncology</i> 2012; 13(10), 993–1001.

Source: Table 2-3, pp46-49 of the submission.

6.8 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ Median-duration of follow up ^a	Risk of bias	Patient population	Outcome(s)
Fruquintinib versus Placebo					
FRESCO 2	691; FRU=461 PBO=230	R, DB, MN, MC, phase III; 11.3 months	Low	Patients with refractory mCRC who had received all current standard approved cytotoxic and targeted therapies and progressed on or were intolerant to TRI/TIP or regorafenib, or both.	OS, PFS, EORTC QLQ-C30 EQ-5D, time to worsening of ECOG PS, and safety
FRESCO 1	416; FRU=278 PBO=138	R, DB, MC, phase III; 13.31 months	Low	Patients with mCRC who had previously received and failed at least two standard chemotherapy lines for mCRC	OS, PFS, and safety
2012-013-00CH1	71; FRU=47 PBO=24	R, DB, MC, phase II; NR	Low	Patients with mCRC who had failed at least two standard chemotherapy lines.	OS, PFS, and safety
Meta-analysis		Included all three trials; assessed OS, PFS, and time to worsening of ECOG PS			
Trifluridine/tipiracil versus Placebo					
RECOURSE	800; TRI/TIP=534 PBO=266	R, DB, MN, MC, phase III; 11.8 months	Low	Patients with refractory mCRC who had received and failed at least two prior regimens of standard chemotherapies for mCRC, and for patients with KRAS wild-type tumours cetuximab or panitumumab.	OS, PFS, time to worsening of ECOG PS, and safety
TERRA	406; TRI/TIP=271 PBO=135	R, DB, MN (Asia only) MC, phase III; 13.8 months	Low	Patients who were refractory or intolerant to at least two prior regimens of standard chemotherapies for mCRC.	OS, PFS, and safety
J003	169; TRI/TIP=112 PBO=57	R, DB, MC, phase II; 11.3 months	Low	Patient with mCRC who had failed two or more standard chemotherapeutic regimens.	OS, PFS, and safety
Meta-analysis		Included all three trials; assessed OS, PFS, and time to worsening of ECOG PS			

Source: Table 2-4, p54; Table 2-8, pp71-73 and Table 2-10, p76 of the submission.

DB = double blind; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D, Euro QoL = 5-dimensional QoL measurement; FRU = fruquintinib; KRAS = Kristen Rat Sarcoma Viral oncogene homolog; MC = multi-centre; mCRC = metastatic colorectal cancer; MN = multi-national; ; N = total participants in group; NR = not reported; OL = open label; OS = overall survival; PBO = placebo; PFS = progression-free survival; R = randomised; TRI/TIP = trifluridine/tipiracil.

^a Median duration of follow-up is reported for the treatment arm of each trial.

6.9 The included trials differed in the following eligibility criteria, which may impact on the exchangeability of the trials for the ITC analysis:

- Both FRESCO 2 (81%) and RECOURSE (58%) were international trials conducted within a largely Caucasian population, whereas the populations in the FRESCO 1, 2012-0013-00CH1, TERRA and J003 trials were 100% Asian (China in FRESCO 1 and 2012-0013-00CH1; China, Korea, and Thailand in TERRA; and Japan in J003). An applicability issue with these trials is that they only enrolled Asian patients.
- All trials required patients to have histologically or cytologically confirmed mCRC that progressed following at least two standard chemotherapy regimens. However, the FRESCO 2 trial required patients to have also progressed on or been intolerant to TRI/TIP or regorafenib. Additionally, patients with deficient mismatch

repair (dMMR) or microsatellite instability-high (MSI-H) tumours had to have received an immune checkpoint inhibitor, and those with *BRAFV600E*-mutant tumours needed prior treatment with a BRAF inhibitor, if approved and locally available, in FRESCO 2.

- FRESCO 1, 2012-0013-00CH1, TERRA and J003 trials did not require patients to have previously received treatment with an anti-VEGF therapy or, if they were *RAS*-wild type (WT), an anti-EGFR therapy.

6.10 The key differences in the baseline characteristics and treatments across FRESCO 2 and RECURSE trials that may have affected the transitivity assumptions of the main ITC analysis include race, performance status, proportion of patients with Kristen Rat Sarcoma Viral oncogene homolog - wild type (*KRAS*-WT) mutation status, prior treatments, number of lines of prior treatments and post progression therapies. Specifically:

- Patients received prior treatment with TRI/TIP (52%), regorafenib (8%) or both (39%) in the FRESCO 2 trial compared to only regorafenib (19%) in RECURSE. The subgroup analyses from FRESCO 2 showed that patients who received both regorafenib and TRI/TIP had relatively improved OS (HR of 0.60 vs. 0.66) and PFS (HR of 0.29 vs. 0.32) compared to the intention-to-treat (ITT) population; this may favour fruquintinib.
- RECURSE (42%) had a higher proportion of patients who received one or more systemic cancer therapies post-progression in the trial compared to FRESCO 2 trial (32%). This difference could impact the ITC results; however, the net impact of the above imbalance was uncertain.

6.11 A claim of non-inferiority for fruquintinib over TRI/TIP was based on the efficacy and safety outcomes of OS, PFS, time to worsening of ECOG PS, and adverse events (AEs). Health-related Quality of Life (HRQoL) data were only available from the FRESCO 2 trial, which used the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and Euro-QoL, 5-dimensional Quality of Life measurement (EQ-5D-5L) questionnaires. The submission did not present objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) from any of the included trials.

6.12 The submission stated that a minimal clinically important difference (MCID) for the treatment of refractory mCRC has not been established. It outlined that a consensus of Canadian medical oncologists, convened by Colorectal Cancer Canada, recommended a median OS of at least two months or a HR of 0.75 or lower for a clinically meaningful benefit in the chemo-refractory setting. Additionally, the submission highlighted that the PBAC also considered the median gain in OS of 2.0 months (HR = 0.69; 95% CI: 0.59, 0.81) in the RECURSE trial (data cut-off: October 2014) to be modest and that, in the context of limited treatment options, the small treatment benefit of TRI/TIP may be meaningful for some patients (paragraph 5.3, TRI/TIP PSD, July 2018 PBAC meeting).

6.13 The submission did not propose a non-inferiority margin. The absence of a noninferiority margin makes it difficult to assess the non-inferiority claim with certainty.

Comparative effectiveness

6.14 The results of OS for the direct and indirect comparisons are presented in Table 4.

Table 4: Results of OS across the trials

Trial ID	Intervention		Placebo		Absolute difference in median ^a	Hazard ratio (95% CI)
	n with event / N (%)	Median OS (months) (95% CI)	n with event / N (%)	Median OS (months) (95% CI)		
Fruquintinib trials						
FRESCO 2	317/461 (68.8%)	7.4 (6.7, 8.2)	173/230 (75.2%)	4.8 (4.0, 5.8)	2.6 months	0.66 (0.55, 0.80)
FRESCO 1	188/278 (67.6%)	9.3 (8.2, 10.5)	109/138 (79.0%)	6.6 (5.9, 8.1)	2.7 months	0.65 (0.51, 0.83)
2012-013-00CH1	38/47 (80.9%)	7.7 (6.9, 10.3)	19/24 (79.2%)	5.5 (3.6, 11.3)	2.2 months	0.71 (0.38, 1.34)
Meta-analysis of fruquintinib trials (Chi ² = 0.08; I ² = 0%; P= 0.96)						0.66 (0.57, 0.76)
Trifluridine/tipiracil trials						
RECOURSE	364/534 (68.2%)	7.1 (6.5, 7.8)	210/266 (78.9%)	5.3 (4.6, 6.0)	1.8 months	0.68 (0.58, 0.81)
TERRA	205/271 (75.7%)	7.8 (7.1, 8.8)	111/135 (82.2%)	7.1 (5.9, 8.2)	0.7 month	0.79 (0.62, 0.99)
J003	75/112 (67.0%)	9.0 (7.3, 11.3)	48/57 (84.2%)	6.6 (4.9, 8.0)	2.4 months	0.56 (0.39, 0.81)
Meta-analysis of TRI/TIP trials (Chi ² = 2.51; I ² = 20%; P= 0.29)						0.69 (0.60, 0.80)
Main ITC (fruquintinib [FRESCO 2] vs. TRI/TIP [RECOURSE])						0.97 (0.76, 1.25)
ITC sensitivity analysis (fruquintinib [meta-analysis] vs. TRI/TIP [meta-analysis])						0.96 (0.78, 1.17)

Source: Table 2-14, p90; Table 2-17, p96; Table 2-19, p99; Table 2-21, p102; Table 2-24, p106; Table 2-26, p108; Table 2-25, p163 and Figure 2-51, p158 of the submission.

CI = confidence interval, ITC = indirect treatment comparison; n = number of participants reporting data, N = total participants in group, OS = overall survival; TRI/TIP = trifluridine/tipiracil.

Bold indicates statistically significant results.

^a Calculated during the evaluation.

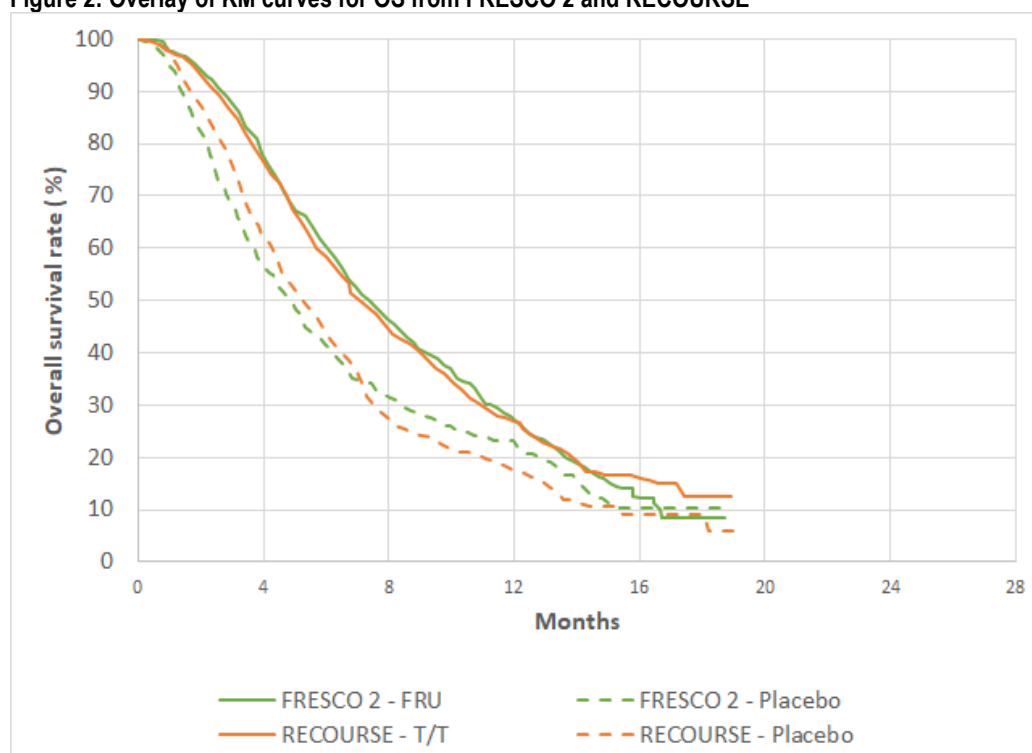
6.15 The results of the OS analysis showed that fruquintinib was associated with a statistically significant reduction in the risk of death compared to placebo in both the FRESCO 2 (34%) and FRESCO 1 (35%) trials. In the 2012-013-00CH1 trial, there was a similar reduction in the risk of death compared to placebo (29%) although this was not statistically significant likely due to the small sample size. The meta-analysis of the three fruquintinib trials estimated a HR of 0.66 (95% CI: 0.57, 0.76), consistent with the results from FRESCO 2 (HR = 0.66; 95% CI: 0.55, 0.80). No statistically significant heterogeneity was detected across the fruquintinib trials (I²=0%, p=0.96). Overall, the results of the OS analysis were similar across the three trials. The OS benefit with fruquintinib compared to placebo was a median increase of 2.6 months in FRESCO 2 trial and 2.7 months in the FRESCO 1 trial.

6.16 Numerically, the median OS was longer in the fruquintinib and placebo arms of FRESCO 1 compared to FRESCO 2 (9.3 months for the drug and 6.6 for placebo vs. 7.4

months for the drug and 4.8 months for placebo). This may suggest better prognosis in Asian patients compared to other populations.

- 6.17 Treatment with TRI/TIP was also associated with a statistically significant reduction in the risk of death in the RECOURSE (32%), TERRA (21%) and J003 (44%) trials. The meta-analysis of the three TRI/TIP trials estimated a HR of 0.69 (95% CI: 0.60, 0.80), which was consistent with the results from the RECOURSE trial (HR = 0.68; 95% CI: 0.58, 0.81). The heterogeneity was low across the three TRI/TIP trials and not statistically significant ($I^2=20%$, $p=0.29$), although there was more heterogeneity than in the fruquintinib trials (paragraph 6.15).
- 6.18 The results of the main ITC between fruquintinib and TRI/TIP, based on the FRESCO 2 and RECOURSE trials, found no statistically significant differences in OS between the two treatments (HR = 0.97; 95% CI: 0.76, 1.25). The results of the sensitivity analysis for OS (ITC using meta-analyses) were consistent with the main ITC analysis (HR = 0.96; 95% CI: 0.78, 1.17). The results of the ITC analysis remained consistent when updated data from the RECOURSE trial (data cut-off: October 2014) was incorporated (HR = 0.96 (95% CI: 0.75, 1.22)).
- 6.19 Figure 2 presents an overlay of the Kaplan-Meier (KM) curves for OS from the FRESCO 2 and RECOURSE trials. The overlaid KM curves from FRESCO 2 and RECOURSE trials illustrated that OS was similar between fruquintinib and TRI/TIP at all timepoints.

Figure 2: Overlay of KM curves for OS from FRESCO 2 and RECOURSE



Source: Figure 2-53, p163 of the submission. FRU = fruquintinib; KM= Kaplan-Meier; OS = overall survival; TRI/TIP = trifluridine/tipiracil.

6.20 The results of the PFS analysis for the direct and indirect comparisons are presented in Table 5.

Table 5: Results of PFS across the trials

Trial ID	Intervention		Placebo		Absolute difference in median ^a	Hazard ratio (95% CI)
	n with event / N (%)	Median PFS (months) (95% CI)	n with event / N (%)	Median PFS (months) (95% CI)		
Fruquintinib trials						
FRESCO 2	392/461 (85.0%)	3.7 (3.5, 3.8)	213/230 (93.0%)	1.8 (1.8, 1.9)	1.9 months	0.32 (0.27, 0.39)
FRESCO 1	235/278 (84.5%)	3.7 (3.7, 4.6)	125/138 (90.6%)	1.8 (1.8, 1.8)	1.9 months	0.26 (0.21, 0.34)
2012-013-00CH1	36/47 (76.6%)	4.7 (2.9, 5.6)	21/24 (87.5%)	1.0 (1.0, 1.6)	3.7 months	0.30 (0.15, 0.59)
Meta-analysis of fruquintinib trials (Chi ² = 2.15; I ² = 7%; P= 0.34)						0.29 (0.25, 0.34)
Trifluridine/tipiracil trials						
RECOURSE	472/534 (88.4%)	2.0 (1.9, 2.1)	251/266 (94.4%)	1.7 (1.7, 1.9)	0.3 month	0.48 (0.41, 0.57)
TERRA	NR	2.0 (1.9, 2.8)	NR	1.8 (1.7, 1.8)	0.2 month	0.43 (0.34, 0.54)
J003	NR	2.0 (1.9, 2.8)	NR	1.0 (1.0, 1.0)	1.0 month	0.41 (0.28, 0.59)
Meta-analysis of TRI/TIP trials (Chi ² = 0.94; I ² = 0%; P= 0.62)						0.46 (0.40, 0.52)
Main ITC (fruquintinib [FRESCO 2] vs. TRI/TIP [RECOURSE])						0.67 (0.43, 1.04)
ITC sensitivity analysis (fruquintinib [meta-analysis] vs. TRI/TIP [meta-analysis])						0.63 (0.52, 0.77)

Source: Table 2-15, p91; Table 2-18, p97; Table 2-20, p100; Table 2-22, p103; Table 2-25, p107; Table 2-27, p109, Table 2-53, p164; Figure 2-52, p159; and Table 2-52, p163 of the submission.

CI = confidence interval, ITC = indirect treatment comparison; n = number of participants reporting data, N = total participants in group, PFS = progression-free survival; TRI/TIP = trifluridine/tipiracil.

Bold indicates statistically significant results.

^a Corrected and calculated during evaluation.

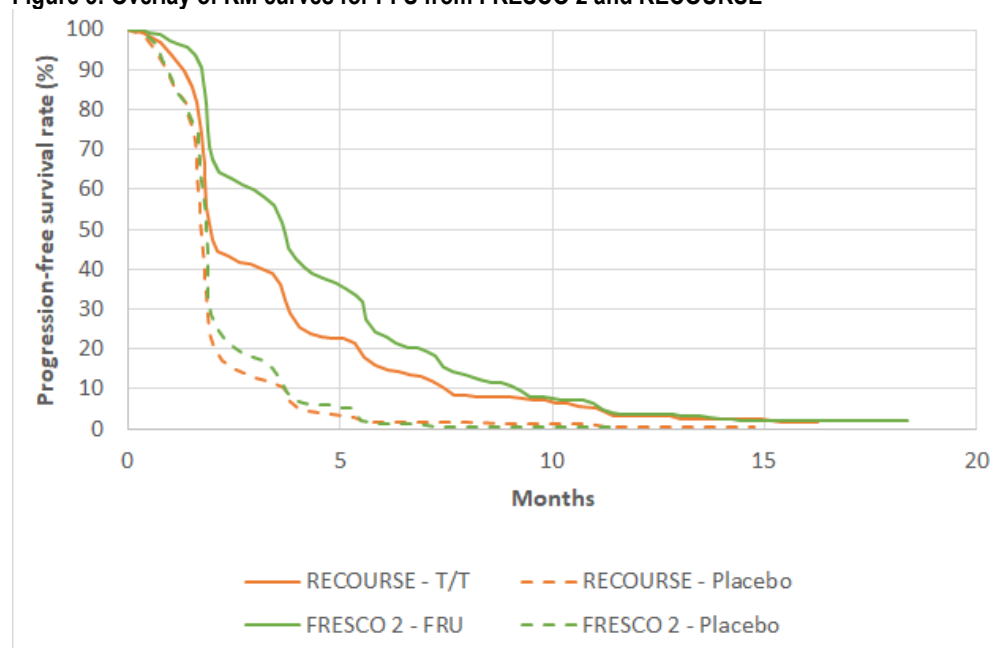
6.21 All three trials of fruquintinib showed statistically significant improvement in PFS for patients in the fruquintinib arm compared to the placebo arm. The meta-analysis of the three fruquintinib trials estimated a HR of 0.29 (95% CI: 0.25, 0.34), consistent with the results from FRESCO 2 (HR = 0.32; 95% CI: 0.27, 0.39). The heterogeneity was low across the three trials and not statistically significant (I²=7%, p=0.34).

6.22 Treatment with TRI/TIP in the RECOURSE, TERRA and J003 trial was also associated with a statistically significant improvement in PFS compared to the placebo arm.

6.23 The results of the main ITC between fruquintinib and TRI/TIP, based on the FRESCO 2 and RECOURSE trials, found no statistically significant differences in PFS between the two treatments (HR = 0.67; 95% CI: 0.43, 1.04). However, the results of the sensitivity analysis for PFS showed statistically significant difference between fruquintinib and TRI/TIP, in favour of fruquintinib.

6.24 Figure 3 presents an overlay of the KM curves for PFS from the FRESCO 2 and RECOURSE trials.

Figure 3: Overlay of KM curves for PFS from FRESCO 2 and RECOURSE



Source: Figure 2-54, p164 of the submission.

FRU = fruquintinib; KM= Kaplan-Meier; PFS = progression-free survival; T/T = trifluridine/tipiracil.

6.25 The results of the direct and indirect comparison of time to worsening of ECOG PS (score ≥ 2), based on the FRESCO 2 and RECOURSE trials only, are summarised in Table 6.

Table 6: Results of time to worsening of ECOG PS (score ≥ 2)

Trial ID	Intervention		Placebo		Absolute difference in median ^c	Hazard ratio (95% CI)
	n with event / N (%)	Median time to ECOG PS worsening (months) (95% CI)	n with event / N (%)	Median time to ECOG PS worsening (months) (95% CI)		
FRESCO 2 ^a	354/461 (76.8%)	5.3 (4.5, 5.8)	183/230 (79.6%)	2.9 (2.5, 3.5)	2.4 months	0.64 (0.53,0.77)
RECOURSE ^b	383/534 (71.7%)	5.7 (NR)	216/266 (81.2%)	4.0 (NR)	1.7 months	0.66 (0.56, 0.78)
ITC Analysis 2 ^b (fruquintinib [FRESCO 2] vs. TRI/TIP [RECOURSE])						0.97 (0.75, 1.24)

Source: Table 2-16, p94; Table 2-23, p105; Table 2-54, p165; of the submission.

CI = confidence interval; ITC = indirect treatment comparison; n = number of participants reporting data; N = total participants in group; NR = not reported; PFS = progression-free survival; TRI/TIP = trifluridine/tipiracil.

Bold indicates statistically significant results.

Italics

^a Analysis 2 uses the 'Time (months) to First Occurrence of an ECOG PS ≥ 2 or Death outcome'.

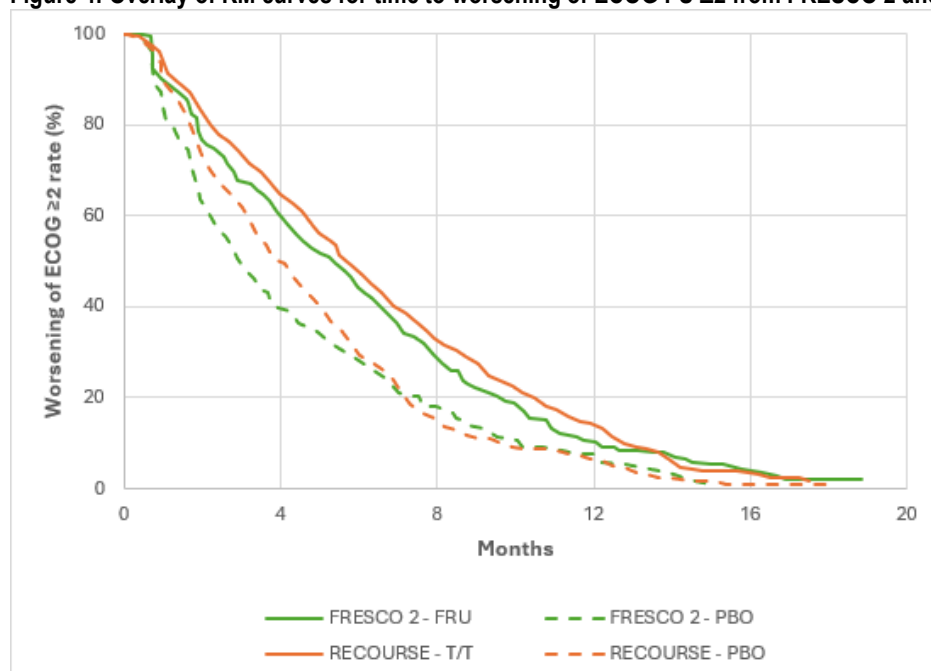
^b In both analyses, time to worsening of ECOG PS in the RECOURSE trial was defined the time between randomisation and assessed as having an ECOG PS ≥ 2 (no further information available).

^c Calculated during the evaluation.

6.26 Treatment with fruquintinib compared with placebo led to a statistically significant delay in the onset of ECOG PS ≥ 2 , with a median difference of 2.4 months. Similarly, treatment with TRI/TIP compared with placebo significantly delayed the time to the first occurrence of ECOG PS ≥ 2 , with a median difference of 1.7 months.

6.27 The ITC analysis for time to worsening of ECOG PS ≥ 2 showed no statistically significant difference between fruquintinib and TRI/TIP (HR = 0.97; 95% CI 0.75, 1.24). Figure 4 presents an overlay of the KM curves for time to worsening of ECOG PS ≥ 2 from the FRESCO 2 (including all deaths in the trial) and RECURSE trials.

Figure 4: Overlay of KM curves for time to worsening of ECOG PS ≥ 2 from FRESCO 2 and RECURSE

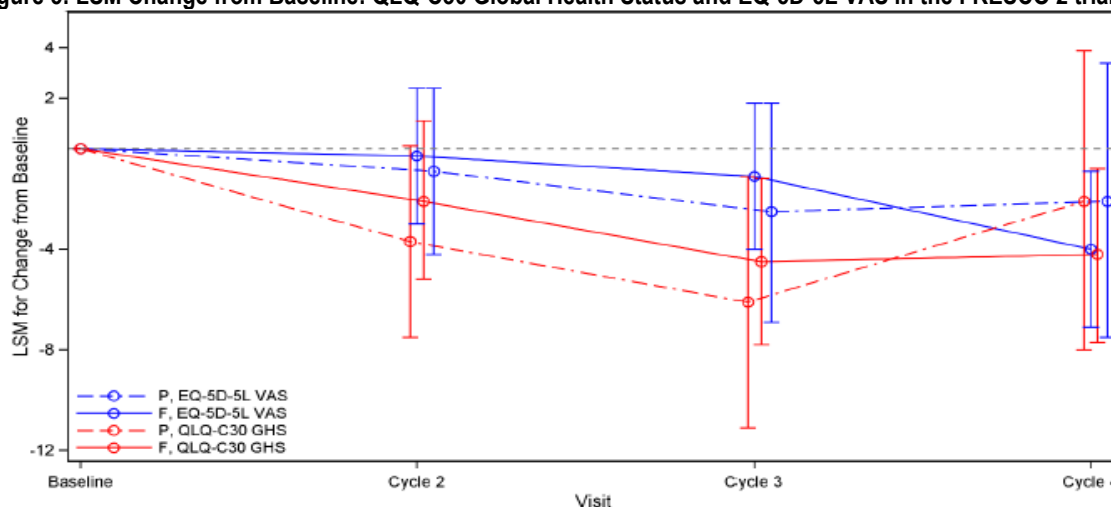


Source: Figure 2-54, p165 of the submission.

ECOG PS = Eastern Cooperative Oncology Group performance status; FRU = fruquintinib; KM= Kaplan-Meier; PBO = placebo; PFS = progression-free survival; T/T = trifluridine/tipiracil.

6.28 The Least Square Mean (LSM) change from baseline for QLQ-C30 Global Health Status (GHS) and EQ-5D-5L visual analogue scale (VAS) in the FRESCO 2 trial is presented in Figure 5. QLQ-C30 global health status scores were similar between the fruquintinib and placebo arms at baseline. HRQoL data was not available for TRI/TIP.

Figure 5: LSM Change from Baseline: QLQ-C30 Global Health Status and EQ-5D-5L VAS in the FRESCO 2 trial



Source: Figure 2-12, p93 of the submission.

F = fruquintinib; GHS = global health status; ITT = intention-to-treat; LSM = least squares mean; P = placebo; VAS = Visual Analogue Scale.

Comparative harms

6.29 A summary of clinical treatment emergent adverse events (TEAEs) reported in the FRESCO 2 and RECOURSE trials are presented in Table 7.

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Table 7: Summary of key adverse events in the fruquintinib and TRI/TIP trials

Trial ID	Intervention n/N (%)	Placebo n/N (%)	RR (95% CI)	RD (95% CI)
FRESCO 2 (fruquintinib versus placebo)				
Any cause TEAE	451/456 (98.90%)	213/230 (92.61%)	1.07 (1.03, 1.11)	0.06 (0.04, 0.09)
Study drug related TEAE	395/456 (86.62%)	130/230 (56.52%)	1.53 (1.36, 1.73)	0.30 (0.23, 0.37)
Any cause severe (Grade ≥3) TEAE	286/456 (62.72%)	116/230 (50.43%)	1.24 (1.07, 1.44)	0.12 (0.04, 0.20)
Study drug related severe (Grade ≥ 3) TEAE	164/456 (35.96%)	26/230 (11.30%)	3.18 (2.17, 4.66)	0.25 (0.18, 0.32)
• Hypertension	49/456 (10.75%)	2/230 (0.87%)	12.36 (3.03, 50.36)	0.10 (0.06, 0.14)
• PPE	28/456 (6.14%)	0/230 (0%)	Not estimable	0.06 (0.03, 0.09)
• Asthenia	24/456 (5.26%)	3/230 (1.30%)	4.04 (1.23, 13.26)	0.04 (0.01, 0.07)
Any cause serious TEAE (SAE)	172/456 (37.72%)	88/230 (38.26%)	0.99 (0.81, 1.21)	-0.01 (-0.08, 0.07)
Study drug related serious TEAE (SAE)	43/456 (9.43%)	8/230 (3.48%)	2.71 (1.30, 5.67)	0.06 (0.02, 0.10)
Any cause AE leading to discontinuation	93/456 (20.39%)	49/230 (21.30%)	0.96 (0.70, 1.30)	-0.01 (-0.07, 0.06)
Study drug related AE leading to discontinuation	45/456 (9.87%)	7/230 (3.04%)	3.24 (1.49, 7.08)	0.07 (0.03, 0.11)
Grade 5 AE leading to death	49/456 (10.75%)	45/230 (19.57%)	0.55 (0.38, 0.80)	-0.09 (-0.14, -0.03)
Study drug related Grade 5 AE leading to death	1/456 (0.22%)	1/230 (0.43%)	0.50 (0.03, 8.03)	0.00 (-0.01, 0.01)
RECOURSE (TRI/TIP versus placebo)				
Any cause TEAE	524/533 (98.31%)	247/265 (93.21%)	1.05 (1.02, 1.09)	0.05 (0.02, 0.08)
Study drug related TEAE	457/533 (85.74%)	145/265 (54.72%)	1.57 (1.40, 1.76)	0.31 (0.25, 0.37)
Any cause severe (Grade ≥3) TEAE	370/533 (69.42%)	137/265 (51.70%)	1.34 (1.18, 1.53)	0.18 (0.11, 0.25)
Study drug related severe (Grade ≥ 3) TEAE	261/533 (48.97%)	26/265 (9.81%)	4.99 (3.43, 7.26)	0.39 (0.32, 0.46)
• Neutrophil count decreased	83/533 (15.57%)	0/265 (0%)	Not estimable	0.16 (0.11, 0.20)
• Neutropenia	107/533 (20.08%)	0/265 (0%)	Not estimable	0.20 (0.15, 0.25)
• Anaemia	65/533 (12.20%)	5/265 (1.89%)	6.46 (2.63, 15.86)	0.10 (0.06, 0.14)
• WBC decreased	52/533 (9.76%)	0/265 (0%)	Not estimable	0.10 (0.06, 0.13)
Any cause serious TEAE (SAE)	158/533 (29.64%)	89/265 (33.58%)	0.88 (0.71, 1.09)	-0.04 (-0.11, 0.03)
Study drug related serious TEAE (SAE)	50/533 (9.38%)	1/265 (0.38%)	24.86 (3.45, 178.97)	0.09 (0.05, 0.13)
Any cause AE leading to discontinuation	55/533 (10.32%)	36/265 (13.58%)	0.76 (0.51, 1.13)	-0.03 (-0.08, 0.01)
Grade 5 AE leading to death	17/533 (3.19%)	30/265 (11.32%)	0.28 (0.16, 0.50)	-0.08 (-0.12, -0.05)
Study drug related Grade 5 AE leading to death	1/533 (0.19%)	0/265 (0%)	Not estimable	0.00 (0.00, 0.01)

Source: Table 2-28, p113, Table 2-31, p119; Table 2-40, p134 and Table 2-43, p139 of the submission.

AE = adverse event; CI = confidence interval; n = number of participants reporting data; N = total participants in group; OR = odds ratio; PPE = palmar-plantar erythrodysesthesia syndrome; RD = risk difference; RR = relative risk; SAE = serious adverse event; TEAE = treatment emergent adverse event; WBC = white blood cells; TRI/TIP = trifluridine/tipiracil.

Bold indicates statistically significant results.

- 6.30 In the FRESCO 2 trial, almost all patients had at least one TEAE in the fruquintinib arm compared to placebo arm (99% vs. 93%). A higher proportion of patients in the fruquintinib arm experienced study drug-related TEAE (87% vs. 57%), study drug-related TEAEs Grade ≥ 3 (36% vs. 11%), and study drug-related serious TEAEs (9% vs. 4%) compared to the placebo arm. The incidence of study drug-related TEAEs in both fruquintinib and placebo arms of FRESCO 1 (96% vs. 70%) and 2012-013-00CH1 (94 vs. 58%) was relatively higher compared to FRESCO 2 (87% vs. 57%), however, the AE profile for fruquintinib was largely consistent across these trials.
- 6.31 In the FRESCO 2 trial, the most frequently reported TEAEs of any grade in $\geq 20\%$ of patients (in the fruquintinib group compared with the placebo group, respectively) were hypertension (37% vs. 9%), asthenia (34% vs. 23%), decreased appetite (27% vs. 17%), diarrhoea (24% vs. 10%), hypothyroidism (21% vs. 0.4%), and fatigue (20% vs. 16%). In the fruquintinib group compared with the placebo group, the most frequently reported study drug-related TEAEs Grade ≥ 3 were hypertension (11% vs. 1%), palmar-plantar erythrodysesthesia syndrome (PPE; 6% vs. 0%), asthenia (5% vs. 1%), fatigue (3% vs. $<1\%$), and diarrhoea (3% vs. 0%). There was one study drug related death in the fruquintinib arm due to intestinal perforation. In general, the rates of all-cause TEAEs were much higher within the individually reported categories compared with TEAEs attributed to the study drug (fruquintinib).
- 6.32 In the RECOURSE trial, almost all patients had at least one TEAE in the TRI/TIP arm compared to placebo arm (99% vs. 93%). Study drug related TEAEs Grade ≥ 3 were higher in the TRI/TIP arm compared to the placebo arm (49% vs. 10%). In the TERRA trial, a higher proportion of patients in the TRI/TIP arm experienced study drug related TEAEs Grade ≥ 3 (46% vs. 10%), consistent with the RECOURSE trial. Safety data from J003 was limited.
- 6.33 In the RECOURSE trial, the most frequently reported TEAEs of any grade in $\geq 10\%$ of patients (in the TRI/TIP group compared with the placebo group, respectively) were nausea (48% vs. 24%), anaemia (40% vs. 8%), decreased appetite (39% vs 29%), fatigue (35% vs. 23%), diarrhoea (32% vs 13%), neutropenia (29% vs 0%), neutrophil count decreased (28% vs. $<1\%$), vomiting (28% vs 14%), and WBC decreased (27% vs. $<1\%$). In the TRI/TIP group compared with the placebo group, the most frequently reported study drug related TEAEs Grade ≥ 3 were a decreased neutrophil count (16% vs. 0%), neutropenia (20% vs. 0%), anaemia (12% vs. 2%), and decreased white blood cell counts (10% vs. 0%). Only one treatment-related death due to Klebsiella pneumonia/septic shock was reported for the TRI/TIP arm. In general, the rates of all-cause TEAEs were much higher within the individually reported categories compared with TEAEs attributed to the study drug (TRI/TIP).
- 6.34 Fruquintinib and TRI/TIP have distinct safety profiles. The most common Grade ≥ 3 AEs with fruquintinib in FRESCO 2 were hypertension, asthenia and hand-foot syndrome, whereas myelosuppression (e.g., neutropenia and anaemia) was the most common Grade ≥ 3 AE reported for TRI/TIP in the RECOURSE trial.

- 6.35 Approximately 20% of patients who received fruquintinib in the FRESCO 2 trial discontinued treatment due to any cause TEAEs, with 10% discontinuing due to study drug related TEAEs. In contrast, 10% of patients receiving TRI/TIP discontinued treatment in RECOURSE trial due to any cause TEAEs. Additionally, 24% of the patients who received fruquintinib in the FRESCO 2 trial required dose reduction due to any cause TEAEs, with 20% requiring dose reduction due to study drug related TEAEs. In the RECOURSE trial, approximately 14% of patients in the TRI/TIP arm required dose reduction due to any cause TEAEs.
- 6.36 The submission conducted an ITC of safety (data not shown) between fruquintinib (via the FRESCO 2 trial) and TRI/TIP (via the RECOURSE trial). Based on the ITC of safety in terms of TEAE, there were no statistically significant differences between the treatments, except for study drug-related TEAEs \geq Grade 3 (OR = 0.50; 95% CI: 0.27, 0.94 and RD = -0.14; 95% CI: -0.24, -0.04) and any cause serious TEAEs (OR = 0.11; 95% CI: 0.01, 0.89 and RR 0.11; 95% CI: 0.01, 0.9), both of which were statistically significant in favour of fruquintinib.
- 6.37 Based on the ITC of safety in terms of worst grade any-cause toxicity, there were no statistically significant differences between fruquintinib and TRI/TIP, except for Grade 4 TEAEs. Statistically significantly fewer patients treated with fruquintinib experienced a Grade 4 TEAE (RD = -0.10; 95% CI: -0.15, -0.05) compared to TRI/TIP; although, neither the OR nor RR was statistically significant. It is important to note that the safety analyses were conducted post-hoc and may lack power to detect statistically significant difference.
- 6.38 Overall, given the differences in the safety profiles as discussed in paragraph 6.34 and the potential transitivity issues across the trials included in the ITC as outlined in paragraph 6.10, it was difficult to assess the comparative safety between fruquintinib and TRI/TIP.

Benefits/harms

- 6.39 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.40 The submission described fruquintinib as non-inferior in terms of effectiveness compared to TRI/TIP. This claim may be supported by the evidence provided in the submission within the confines of the defined comparison (fruquintinib versus TRI/TIP in patients who have received at least two prior therapies for mCRC), but the following uncertainties remain:
- Clinical evidence from FRESCO 1 supports the 3L use of fruquintinib as an alternative to TRI/TIP; however, the trial only enrolled Chinese patients. Given the population in FRESCO 2 was pre-treated with TRI/TIP, the clinical evidence presented from FRESCO 2 is more relevant to inform decision-making regarding

the use of fruquintinib subsequent to TRI/TIP. Notwithstanding, the results of the FRESCO 1 and FRESCO 2 trials were similar with respect to OS and PFS, as noted by the PSCR.

- The results of the main ITC (fruquintinib FRESCO 2 trial versus TRI/TIP RECOURSE trial) were subject to a potentially high risk of bias due to transitivity issues across the trials in terms of gender, race, performance status, prior treatments, KRAS mutation status, and post-progression treatments. The PSCR noted that the similarity of the OS and PFS curves in the placebo arms of the FRESCO 2 and RECOURSE trials indicate that differences in trial populations at baseline may not have been clinically relevant and unlikely to confound the indirect estimates of comparative treatment effect.
- 6.41 The PSCR emphasised that the evidence base that exists for both the proposed 3L setting (FRESCO 1), where it will likely replace/displace TRI/TIP, and the 4L setting, where it will be used subsequent to TRI/TIP (FRESCO 2), was a strength of the submission. The Pre-PBAC response noted that in general, treatments listed on the basis of a CMA may not only replace the main comparator but also be used subsequent to it by some patients.
- 6.42 Overall, the ESC considered that the claim of non-inferior efficacy compared to TRI/TIP was reasonable. While the PBAC noted the uncertainty associated with the line of therapy for which fruquintinib will be used in practice and the transitivity issues across the different trial populations, it considered, on balance, that the claim of non-inferior efficacy compared to TRI/TIP was justified.
- 6.43 The submission described fruquintinib as non-inferior in terms of safety compared to TRI/TIP. The evaluation considered that this claim was not adequately supported because fruquintinib and TRI/TIP have distinct safety profiles. In the fruquintinib FRESCO 2 trial, the most common Grade ≥ 3 drug-related TEAEs were hypertension (11%), hand-foot syndrome (6%) and asthenia (5%), whereas in the TRI/TIP RECOURSE trial, myelosuppression events (neutropenia [20%], decrease in neutrophil count [16%], and anaemia [12%]) were the most common Grade ≥ 3 drug-related TEAEs. The PSCR argued that neither toxicity profile is necessarily preferable over the other and there may be broader benefits of having agents with different safety profiles available to patients; in particular, fruquintinib may be more suitable for patients who are more susceptible to myelosuppression. The ESC noted that fruquintinib had fewer severe TEAEs compared to TRI/TIP, but it had more discontinuations of therapy. Overall, the ESC and the PBAC considered that the safety of fruquintinib was different but manageable compared to TRI/TIP.

Economic analysis

- 6.44 The submission presented a CMA of fruquintinib versus TRI/TIP based on the claim of non-inferior efficacy and safety. The CMA presented was based on the published price for TRI/TIP. The evaluation noted that the CMA is only appropriate if the following are

accepted by the PBAC: (i) the place in therapy of fruquintinib is third or later line for metastatic disease; (ii) the appropriate comparator is TRI/TIP; (iii) the FRESCO 1 and FRESCO 2 trial populations are sufficiently representative of the intended fruquintinib PBS population in the 3L setting; and (iv) the clinical claim of non-inferiority in terms of effectiveness and safety is reasonable. The PBAC accepted these conditions.

- 6.45 The PBAC considered that fruquintinib 5 mg/day for 21 days of each 28-day cycle (total 105 mg) is equi-effective to TRI/TIP 60 mg twice daily on days 1-5 and 8-12 of each 28-day cycle (total 1,200 mg).
- 6.46 The equi-effective doses of fruquintinib and TRI/TIP were based on the recommended dosing regimens in the draft PI for fruquintinib and approved TGA PI for TRI/TIP. The recommended dosing regimen for fruquintinib is 5 mg/day for first 21 days of each 28-day cycle, and for TRI/TIP is 35 mg/m² twice daily on days 1-5 and 8-12 of each 28-day cycle. The dosing regimens were consistent with the dosing protocols applied in the FRESCO 2 and RECOURSE trials.
- 6.47 Given that TRI/TIP dosing is based on body surface area, the submission used an average dose of 60 mg for TRI/TIP. The average dose of 60 mg for trifluridine (i.e., 60 mg twice daily on days 1-5 and days 8-12 of each 28-day cycle) was accepted by the PBAC in the November 2016 TRI/TIP submission (paragraph 6.37, TRI/TIP, PSD, November 2016 PBAC meeting). This was reasonable and consistent with dosing used in the regorafenib submission to the PBAC.
- 6.48 The submission assumed treatment duration for fruquintinib and TRI/TIP was the same based on the claim of non-inferior PFS and, therefore, not considered in the CMA. However, there were differences in the treatment duration between the key clinical trials. The mean treatment duration with fruquintinib was 4.04 months (4.34 cycles) in the FRESCO 2 trial, while the mean treatment duration with TRI/TIP was 12.7 weeks or 2.9 months [3.18 cycles (i.e., 12.7/4)] in the RECOURSE trial. The PSCR stated that equal treatment durations for fruquintinib and TRI/TIP is consistent with the submission's claim of non-inferior efficacy and any nominal differences in durations are an artefact of the trial populations and designs.
- 6.49 The submission applied a dose intensity of 100% to both fruquintinib and TRI/TIP rather than the average relative dose intensity (RDI) reported in the FRESCO 2 (92%) and RECOURSE (89%) trials.
- 6.50 The submission stated that, to be conservative, the costs of managing AEs were not included in the CMA. The submission estimated the total cost per cycle for management and monitoring of AEs to be \$6.79 for fruquintinib and \$318.79 for TRI/TIP. Although TRI/TIP may incur higher AE costs due to its safety profile (myelosuppression), these estimates are uncertain because:
- The submission did not justify the use of the criterion for selecting only study-drug related Grade 4 or serious AEs (SAEs) with an occurrence of $\geq 1.5\%$. No AEs in the FRESCO 2 trial met this criterion, whereas the cost of hospitalisation for two SAEs

(febrile neutropenia and anaemia) in the RECURSE trial were included. This may underestimate the treatment cost of AEs associated with fruquintinib.

- The submission did not justify the criterion of selecting concomitant medications that had $\geq 5\%$ higher utilisation in the fruquintinib or TRI/TIP arms of the trials compared to the placebo arms. Furthermore, the submission used an incremental difference approach to calculate the cost of management of AEs, which may not accurately reflect the true burden of AEs in practice and may underestimate treatment costs.

The PBAC did not accept the submission’s position that the AE costs associated with fruquintinib would be lower than those associated with TRI/TIP, as it considered the above assumptions to be unreasonable. The PBAC considered it appropriate that the AE costs are not included in the CMA as they are likely to be similar between agents.

6.51 The results of the CMA based on the published AEMP of TRI/TIP are presented in Table 8.

Table 8: Results of the CMA based on published AEMP of TRI/TIP

	Component	Fruquintinib	Calculation/Reference	Trifluridine/tipiracil	Calculation/Reference
A	Cost per pack	\$█	E/D	\$942.86	PBS item 11542
B	Total mg per pack	105	21 x 5 mg tablets	400	20 x 20 mg tablets
C	Mg required per 28-day treatment cycle	105	21 doses per cycle at 5 mg per dose	1200	20 doses per cycle at an average dose of 60 mg per patient
D	Number of packs required per 28-day treatment cycle	1	C/B	3	C/B
E	Total cost per 28-day treatment cycle	\$█	Equal to cost per 28-day treatment cycle of TRI/TIP	\$2,828.58	A x D

Source: Table 3-6, p219 of the submission and updated to include the published AEMP of TRI/TIP.

AEMP = approved ex-manufacturer price; CMA = cost minimisation approach; TRI/TIP = trifluridine/tipiracil.

6.52 Based on the published price of TRI/TIP, the estimated cost minimised AEMP and DPMQ for fruquintinib was \$█ and \$█, respectively.

6.53 Table 9 presents the results of sensitivity analyses for the CMA conducted during the evaluation.

Table 9: Results of sensitivity analyses using published AEMP of TRI/TIP

Component	Fruquintinib	TRI/TIP	% change from base case
Base case			
Cost per pack AEMP	\$	\$942.86	-
Applying mean duration of treatment reported in the FRESCO 2 (4.34 cycles) and RECOURSE (3.18 cycles) trials			
Cost per pack AEMP	\$	\$942.86	-
Applying RDI reported in FRESCO 2 (91.6%) and RECOURSE (89%) trial			
Cost per pack AEMP	\$	\$942.86	-
Applying both mean duration of treatment and RDI			
Cost per pack AEMP	\$	\$942.86	-
Applying published DPMQ of TRI/TIP to calculate the cost-minimised price of fruquintinib			
Cost per pack AEMP	\$	\$983.40	-

Source: Calculated during evaluation.

AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity; RDI = relative dose intensity; TRI/TIP = trifluridine/tipiracil.

Drug cost/patient/course

6.54 Based on the cost minimised DPMQ of \$ [REDACTED] for fruquintinib (using published prices), the estimated cost per patient per course was \$ [REDACTED]. This was based on a mean treatment duration of 4.04 months (4.34 cycles) observed in the fruquintinib arm of the FRESCO 2 trial.

Estimated PBS usage & financial implications

6.55 This submission was not considered by DUSC.

6.56 The submission used a market share approach to estimate the use and financial impact of listing fruquintinib. The sources of data used in the financial estimates are presented in Table 10.

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Table 10: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Projected use of TRI/TIP	█ ¹ prescriptions; based on prescription data for TRI/TIP from Medicare PBS Statistics Item Reports for the year 2020. The submission assumed that the decrease in use of TRI/TIP in 2021 and 2022 was reversed in 2023 and was expected to return to levels of utilisation recorded in 2019 and 2020 in 2024.	This was uncertain; the use of TRI/TIP was based on data from the year 2020 and assumed to remain constant from year 1 to year 6.
Projected utilisation of fruquintinib	█% in Year 1 increasing to █% in Year 6; based on the Sponsor's assumption.	This was uncertain; no data or evidence was provided to support the assumption.
Duration of therapy and dose of fruquintinib and TRI/TIP	The mean treatment durations of both therapies were assumed to be equal. The dose intensity of both treatments were assumed to be 100%.	This was uncertain as noted for the economic analysis.
Proportion of fruquintinib utilisation in 4L setting	30%; based on the proportion of patients who received subsequent chemotherapy treatment in FRESCO 1 trial (32.4%).	The utilisation of fruquintinib in the 4L may be higher, considering the possible use of TRI/TIP + BEVA in the 3L setting and its effectiveness in the heavily TRI/TIP pretreated population of the FRESCO 2 trial.
Proportion of fruquintinib utilisation as a substitution of TRI/TIP, in the third-line setting	70%; complement of the proportion fruquintinib utilisation in the fourth-line setting.	There is no optimal sequence of treatment in the third line setting for mCRC. Both fruquintinib and TRI/TIP can be used sequentially.
Fruquintinib	Published DPMQ: \$7,299.70 for both 5 mg (1 pack) and 1 mg (4 packs). Cost minimised published DPMQ: \$█ for both 5 mg (1 pack) and 1 mg (4 packs).	The effective price of TRI/TIP was unknown to the sponsor.
TRI/TIP	Published DPMQ: \$2,283.57 for 15 mg/6.14 mg \$3,933.61 for 20 mg/8.19 mg	The effective price of TRI/TIP was unknown to the sponsor.

Source: Table 4-2, p222; Table 4-3, p224 and Table 4-5, p225 of the submission.

BEVA = bevacizumab; DPMQ = Dispensed Price for Maximum Quantity; 3L = third line; 4L = fourth line; mCRC = metastatic colorectal cancer; RDI = relative dose intensity; TRI/TIP = trifluridine/tipiracil.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

6.57 Table 11 presents the estimated financial implications of listing fruquintinib, based on the proposed published price of fruquintinib (cost minimised DPMQ: \$█) and the published price of TRI/TIP (DPMQ: \$3,933.61 for the 20 mg/8.19 mg strength and \$2,283.57 for the 15 mg/6.14 mg strength).

Table 11: Estimated use and financial implications

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)
Estimated extent of use						
Fruquintinib 5 mg	1	2	2	2	2	2
Fruquintinib 1 mg	1	1	1	1	1	1
Net financial implications using the base case cost minimised price of fruquintinib (DPMQ: \$ [redacted] a)						
Net cost to PBS/RPBS (\$)	3	3	3	3	3	3
Sensitivity analysis: net financial implications assuming that 100% fruquintinib utilisation would be in substitution to TRI/TIP (i.e., only in 3L setting) b						
Net cost to PBS/RPBS (\$)	3	3	3	3	3	3

Source: Table 4-11, p229 of the submission.

TRI/TIP = trifluridine/tipiracil.

a The DPMQ of fruquintinib was calculated from the cost minimised AEMP of \$ [redacted]. The submission's nominated published DPMQ of \$7,299.70 was replaced by the cost minimised published DPMQ (\$ [redacted]) for the purposes of calculating the financial estimates in the evaluation.

b Calculated during the evaluation.

Note: The requested published price of fruquintinib (DPMQ \$7,299.70) is considerably higher than the price based on the CMA with the TRI/TIP published price (fruquintinib DPMQ \$ [redacted]).

The redacted values correspond to the following ranges:

1 < 500

2 5,000 to < 10,000

3 \$0 to < \$10 million

6.58 Based on the cost minimised DPMQ (using the published price for TRI/TIP), the total cost to the PBS/RPBS of listing fruquintinib was estimated to be \$0 to < \$10 million in Year 6, and a total of \$0 to < \$10 million in the first six years of listing. Although fruquintinib is cost-minimised to TRI/TIP, it resulted in a net cost to the PBS/RPBS due to its subsequent use in the 4L setting (as well as a small cost due to differences in mark-ups and patient co-payments; see paragraph 6.61 below).

6.59 The utilisation/financial estimates were considered uncertain due to the following issues:

- The total number of prescriptions for TRI/TIP was assumed to remain constant, i.e. 5,000 to < 10,000 prescriptions, from Year 1 to Year 6 and was based on historical prescription data for the year 2020, extracted from the Medicare PBS Statistics Item Reports. The submission anticipated that the utilisation of TRI/TIP in 2024 would return to the levels observed in 2019 and 2020. Based on the recent data from DUSC, the utilisation of TRI/TIP for mCRC appears to be stable.
- The submission did not provide any evidence to support the assumption of [redacted]% market share of fruquintinib in Year 1, increasing to [redacted]% in Year 6.
- The submission assumed that 30% of fruquintinib utilisation would be following TRI/TIP in the 4L setting, based on the proportion of patients who initiated subsequent chemotherapy in the FRESCO 1 trial (32%), while the remaining 70% would substitute TRI/TIP in the 3L setting. However, approximately 42% of patients in fruquintinib arm received at least one subsequent systemic anti-cancer therapy in the FRESCO 1 trial. This was tested as an upper limit of fruquintinib utilisation in a sensitivity analysis (refer to paragraph 6.60). The ESC considered that this was the most important financial issue for consideration.

- The submission assumed that the same treatment duration and dose intensity for both fruquintinib and TRI/TIP.
- 6.60 The submission conducted a sensitivity analysis, assuming 42% fruquintinib utilisation would be used subsequent to TRI/TIP, while 58% utilisation would result in substitution of TRI/TIP. Increasing the utilisation in the fourth-line setting increases the financial estimates by 39%, from \$0 to < \$10 million to \$0 to < \$10 million in the first six years of listing. The ESC and the PBAC noted the increase in cost associated with this scenario.
- 6.61 A sensitivity analysis was conducted by the evaluation using the cost minimised published DPMQ of fruquintinib (\$1), assuming that 100% fruquintinib utilisation would be in substitution to TRI/TIP (i.e., only in 3L setting). This resulted in a cost to the PBS/RPBS: \$0 to < \$10 million in Year 1 increasing to \$0 to < \$10 million in Year 6. This was due to the difference in mark-ups (CMA was conducted at AEMP level instead of DPMQ) and the effect of patient co-payments (the CMA did not include any co-payments).

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing for fruquintinib for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with or who are not considered candidates for fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy. Listing was recommended on a cost-minimisation basis against trifluridine/tipiracil (TRI/TIP).
- 7.2 The PBAC considered that fruquintinib 5 mg/day for 21 days of each 28-day cycle (total 105 mg) is equi-effective to TRI/TIP 60 mg twice daily on days 1-5 and 8-12 of each 28-day cycle (total 1,200 mg).
- 7.3 The PBAC considered that a high clinical need exists for alternative treatments because mCRC is a common cancer and there are limited new therapeutic options for this patient group (outside the uncommon deficient mismatch repair [dMMR] subset). The PBAC noted that current PBS medications are only moderately effective for mCRC and fruquintinib would provide an additional option with a modest benefit to patients in both the 3L and 4L setting. The PBAC noted the consumer comments received for this submission from health care professionals, who emphasised that fruquintinib will potentially fill a gap in effective later-line treatment options. The PBAC also noted the advice received from Bowel Cancer Australia, Rare Cancers Australia, and the MOGA, all of which supported the proposed listing for fruquintinib.
- 7.4 The PBAC noted that the requested restriction reflected that of TRI/TIP for the treatment of mCRC and was consistent with the FRESCO 1 trial, in which patients had previously received and failed at least two standard chemotherapy lines for mCRC.

The requested restriction did not restrict use of fruquintinib to a specific line of treatment (i.e., 3L (replacing or displacing 3L TRI/TIP) or 4L (used subsequent to 3L TRI/TIP)). The PBAC considered that the totality of the clinical evidence for fruquintinib supports a line agnostic listing, i.e. for all patients who will be eligible under the proposed 3L (or later) restriction. The PBAC accepted that proposed restriction aligned with the appropriate clinical place for fruquintinib in the treatment of mCRC.

- 7.5 The submission nominated TRI/TIP as the comparator, as the only PBS-listed treatment option for patients with mCRC who have been treated previously or are not considered suitable for prior therapies listed in paragraph 7.1, and most likely to be replaced by fruquintinib. In November 2021, the PBAC considered TRI/TIP to be the reasonable comparator for this population when considering regorafenib, and considered it to also be the appropriate main comparator for fruquintinib. The PBAC noted that other treatment options for mCRC include regorafenib and TRI/TIP + BEVA. Noting that regorafenib has previously been considered for mCRC (November 2021) and not recommended for listing, the PBAC considered the submission appropriately excluded it as a comparator. While the PBAC considered that TRI/TIP + BEVA could be a reasonable secondary comparator based on favourable data from the SUNLIGHT trial, it noted that listing for combination therapy has not been pursued by TRI/TIP sponsor and its PBS restriction states, “The treatment must be the sole PBS-subsidised therapy for this condition”, precluding use with BEVA on the PBS.
- 7.6 The submission was based on two ITCs between fruquintinib and TRI/TIP, using placebo as the common reference. The main ITC compared fruquintinib (via the FRESCO 2 trial) with TRI/TIP (via the RECURSE trial). The PBAC noted that the FRESCO 2 trial was not the most appropriate for the comparison between fruquintinib and TRI/TIP in the requested 3L setting because fruquintinib patients in FRESCO 2 were required to have already failed TRI/TIP and/or regorafenib. Further, the PBAC noted that the FRESCO 1 trial involved exclusively Chinese patients, which is a potential applicability issue for an Australian population. Notwithstanding, the PBAC acknowledged the overall evidence base from the FRESCO 1 (3L fruquintinib) and FRESCO 2 (4L fruquintinib) trials had similar results for PFS and OS, and on balance, the PBAC considered that the claim of non-inferior efficacy compared to TRI/TIP was justified.
- 7.7 The PBAC considered the claim that fruquintinib is non-inferior in terms of comparative safety compared with TRI/TIP was not adequately supported because fruquintinib and TRI/TIP have distinct safety profiles. Clinical trial data shows that fruquintinib is associated with hypertension, hand-foot syndrome and asthenia, whereas TRI/TIP is associated with myelosuppression events such as neutropenia, decrease in neutrophil count and anaemia. The PBAC noted the Sponsor’s argument that neither toxicity profile is necessarily preferable over the other and there may be broader benefits of having agents with different safety profiles available to patients; in particular, fruquintinib may be more suitable for patients who are more susceptible

to myelosuppression. Overall, the PBAC considered that the safety of fruquintinib was different but manageable compared to TRI/TIP.

- 7.8 The PBAC considered that the CMA should be based on the equi-effective doses of fruquintinib and TRI/TIP, as per paragraph 7.2. The PBAC considered that the costs of managing AEs associated with fruquintinib are likely to be similar to those associated with TRI/TIP, and therefore AE costs were not required to be applied to the CMA. The PBAC noted the relative dose intensity and treatment duration were assumed to be the same for fruquintinib and TRI/TIP. The PBAC considered this assumption, especially in relation to treatment duration, to be uncertain given the differences observed across the trials. The PBAC noted the differences in treatment duration may reflect differences in the patient characteristics across the FRESCO 2 and RECOURSE trials, including line of therapy (paragraph 6.40), and in clinical practice the treatment duration will be impacted by relative use in the 3L versus 4L settings. Given this, the PBAC considered it would be reasonable to assume no difference in the dose intensity and duration of treatment for the purposes of the equi-effective doses.
- 7.9 The market share approach used to estimate the financial impact assumed that 70% of fruquintinib treated patients would substitute for TRI/TIP in the 3L setting and 30% of fruquintinib patients would receive fruquintinib in the 4L setting following TRI/TIP. The PBAC noted that the sequential use of fruquintinib is associated with a net PBS/RPBS cost of approximately \$0 to < \$10 million in the first six years of listing (based on the cost minimised published price of fruquintinib, see paragraphs 6.52 and 6.58), and that this would be lower when using the effective price for TRI/TIP in the cost-minimisation analysis. The PBAC considered that the extent of sequential use of fruquintinib to be uncertain and noted increasing the extent of sequential use to 42%, based on the proportion of patients in FRESCO 1 trial receiving at least one subsequent systemic anti-cancer therapy, increased the financial estimates by 39%. However, the PBAC noted that the absolute increase in cost to government, from \$0 to < \$10 million to \$0 to < \$10 million over the first six years of listing, is relatively small. Overall, the PBAC considered the likely extent of sequential use to be between 30% and 42% of fruquintinib use.
- 7.10 The PBAC advised that fruquintinib is not suitable for prescribing by nurse practitioners. The PBAC noted that TRI/TIP is not available for nurse prescribing.
- 7.11 The PBAC recommended that the Early Supply Rule should not apply to fruquintinib. The PBAC noted that the Early Supply Rule does not apply to TRI/TIP.
- 7.12 The PBAC recommended that fruquintinib should not be treated as interchangeable on an individual patient basis with any other drugs under Section 101 (3BA) of the *National Health Act 1953*.
- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because fruquintinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over TRI/TIP, or not expected to address a high and urgent unmet clinical need given the presence of

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an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.14 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FRUQUINTINIB					
fruquintinib 5 mg capsule, 21	NEW	1	21	5	Fruzaqla®
fruquintinib 1 mg capsule, 21	NEW	4	84	5	Fruzaqla®
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative advice: A patient may only qualify for PBS-subsidised treatment under this restriction once. Following completion of the initial PBS-subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.					
Indication: Metastatic colorectal cancer					
Treatment Phase: Initial PBS-subsidised treatment					
Clinical criteria:					
Patient must have/had a WHO performance status of 1 or less, prior to initiation of treatment with this drug for this condition.					
AND					
Clinical criteria					
Patient must not have previously received PBS-subsidised treatment with this drug for this condition; OR					
Patient must be each of: (i) currently receiving non-PBS subsidised supply for this drug for this PBS indication, (ii) untreated with this drug at the time that non-PBS subsidised supply was commenced, (iii) free of disease progression since commencing non-PBS subsidised supply					
AND					
Clinical criteria:					
Patient must have been previously treated with or not considered a candidate for treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-vascular endothelial growth factor (anti-VEGF) agent and an anti-epidermal growth factor receptor (anti-EGFR) agent for this condition					
AND					
Clinical criteria:					
The treatment must be the sole PBS-subsidised therapy for this condition.					
Prescribing instruction:					

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The patient's WHO performance status and body weight must be documented in the patient's medical records at the time the treatment is initiated.
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Indication: Metastatic colorectal cancer
Treatment Phase: Continuing treatment
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.
AND
Clinical criteria:
Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not develop progressive disease whilst receiving PBS-subsidised treatment with this drug for this condition

8.2 The PBAC recommended flow on changes to existing restriction for trifluridine + tipiracil in mCRC (PBS item codes: 11524M and 11507P).

8.3 The PBAC noted the following flow-on changes:

- Update to the current prescribing instruction to remove the word “cycle”;

Prescribing instruction:
The patient's WHO performance status and body weight must be documented in the patient's medical records at the time the treatment cycle is initiated.

- Update to the clinical criteria to facilitate use in patients been previously treated with or not considered a candidate for all standard therapies.

Clinical criteria:
<ul style="list-style-type: none"> • Patient must have previously received treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-vascular endothelial growth factor (anti-VEGF) agent and an anti-epidermal growth factor receptor (anti-EGFR) agent for this condition; or • Patient must not be a suitable candidate for treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGF agent and an anti-EGFR agent for this condition. <p><i>Patient must have been previously treated with or not considered a candidate for treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-vascular endothelial growth factor (anti-VEGF) agent and an anti-epidermal growth factor receptor (anti-EGFR) agent for this condition</i></p>

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers

applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.